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# The Future of Ischemic Stroke: Flow from Prehospital Neuroprotection to Definitive Reperfusion

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Stroke · Ischemia · Collaterals · Neuroprotection · Reperfusion · Imaging

**Abstract**

Recent advances in ischemic stroke enable a seamless transition of the patient flow from the prehospital setting to definitive reperfusion, without the arbitrary separation of therapeutic phases of ischemia based on time alone. In 2013, the framework to understand and directly address the pathophysiology of cerebral blood flow that determines the timeline or evolution of ischemia in an individual case is given. This continuum of flow and the homeostasis of brain perfusion balanced by collaterals may be captured with serial imaging. Ongoing imaging core laboratory activities permit large-scale measurement of angiographic and tissue biomarkers of ischemia. Prehospital neuroprotection has become a reality and may be combined with revascularization therapies. Recent studies confirm that image-guided thrombolysis may be achieved without restrictive time windows. Baseline imaging patterns may be used to predict response to therapy and serial imaging may discern recanalization and reperfusion. Advanced techniques, such as arterial spin-labeled MRI, may also report hyperperfusion associated with hemorrhagic transformation. Endovascular therapies, including novel stent retriever devices, may augment revascularization and angiographic core laboratories may define optimal reperfusion. Serial evaluation of collaterals and reperfusion may identify definitive reperfusion linked with good clinical outcome rather than imposing arbitrary definitions of effective recanalization. Reperfusion injury and hemorrhagic transformation of various types may be detailed to explain clinical outcomes. Similar approaches may be used in intracranial atherosclerosis where flow, and not the degree of luminal stenosis, is paramount. Fractional flow may

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now be measured with computational fluid dynamics to identify high-risk lesions that require revascularization to restore the equilibrium of antegrade and collateral perfusion. Serial perfusion imaging of such cases may also illustrate inadequate cerebral blood volume gradients that may be more informative than blood flow delay alone. In sum, the growing understanding of collateral perfusion throughout all stages of ischemic stroke provides a framework for the future of ischemic stroke.

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## Introduction

The field of ischemic stroke has been transformed in 2013, as the framework to study cerebral blood flow has been established. Stroke care providers now appreciate that cerebral ischemia is undoubtedly a dynamic process. In this context, there is no need to designate arbitrary separation of different phases of ischemia as hyperacute, acute or subacute. The exact time points are difficult to demarcate, as are the justifications for such time boundaries. There may be general time epochs, but the proper way to understand time is along a continuum of changing blood flow states that evolve over prolonged time periods in any individual. Each patient manifests its own trajectory in terms of survival from ischemia [1].

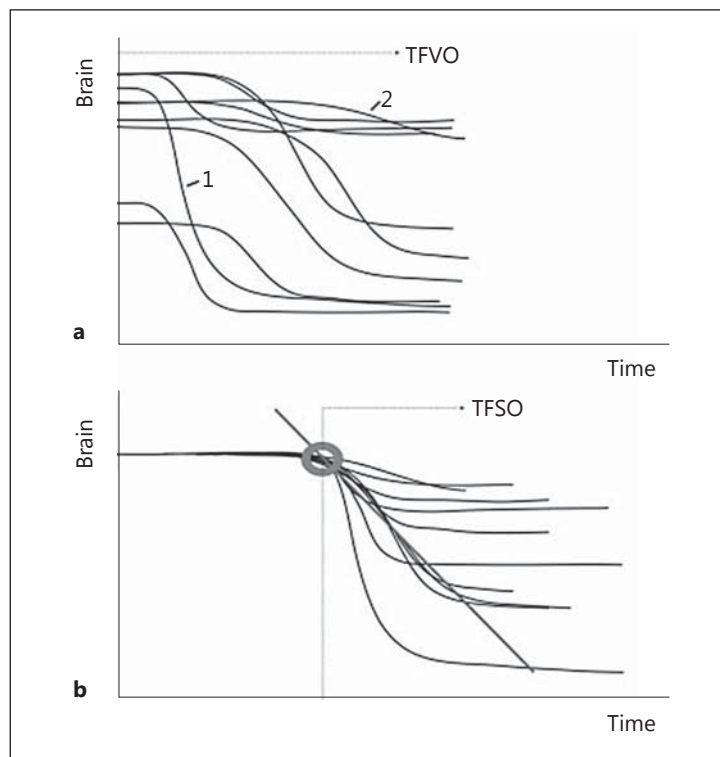
Imaging data at more than one time point for any individual patient, irrespective of the modality of the study, may be illuminating regarding the underlying pathophysiology. Such serial imaging not only illustrates how much ischemic injury has evolved, but it is also important to evaluate the effects of attempted therapeutic interventions, to appreciate the impact of a given therapy and to measure the degree of reperfusion, if any. The infrastructure and technology to assess all these factors through various modalities including serial CT, MRI and angiography are now available.

Against this backdrop, we have witnessed the development of numerous new interventional devices [2–4] to manage acute ischemic stroke. However, defining optimal medical therapy for large artery disease has been challenging. Paradoxically, the ultimate consequence of hypoperfusion, or ischemia, has been largely overlooked and remains untargeted other than via restoration of upstream arterial patency.

### *Time Is NOT Brain!*

Reconsideration of cerebral ischemia as a dynamic and evolving process, unfolding over time, rather than arbitrarily split into artificial time windows, provides insight on the oversimplified notion that time is brain. Although it is true that across populations of stroke cohorts, it is possible to calculate averages for the amount of brain tissue lost or burden of ischemic injury based on different time phases, the course of an individual patient cannot be predicted. Population statistics can yield a specific estimate of cellular injury in the brain, yet one must remember that such an average does not predict the course of an individual patient [1].

Time is routinely used to mark the onset of neurological symptoms, yet the time of symptom onset is almost never equivalent to the time of vascular occlusion. What is regarded as the time from symptom onset directly reflects time from collateral failure, when collaterals can no longer offset or sustain blood flow affected by upstream arterial occlusion [1]. Even with sites of arterial occlusion that may be associated with devastating outcomes, such as middle cerebral artery or internal carotid artery occlusions, other individuals may be completely asymptomatic or solely harbor silent ischemic lesions. This distinction among cases depends completely on the degree of collateral circulation (fig. 1).



**Fig. 1.** Schematic illustration of the relation between time and brain tissue loss, noting marked dissimilarity between **a** pathophysiology measured from time from vascular occlusion (TFVO) and **b** measures utilizing time from symptom onset (TFSO). Each individual curve represents unique temporal features of a particular case, including baseline brain volume, time to symptom onset or collateral failure, degree of collateral dependence influenced by lesion location, and resultant infarct volume. Rapid decompensation caused by poor collaterals in abrupt cardioembolic occlusion (**a**, 1) may lead to large infarcts at very early time points, whereas progressive ischemia and robust collateralization in intracranial atherosclerosis (**a**, 2) may manifest with a long time window and smaller infarct volumes. In the absence of imaging, time alone measured from symptom onset (**b**, circle) is often used to group these identical curves and calculate brain lost based on a linear, rather than a biologically plausible sigmoid model.

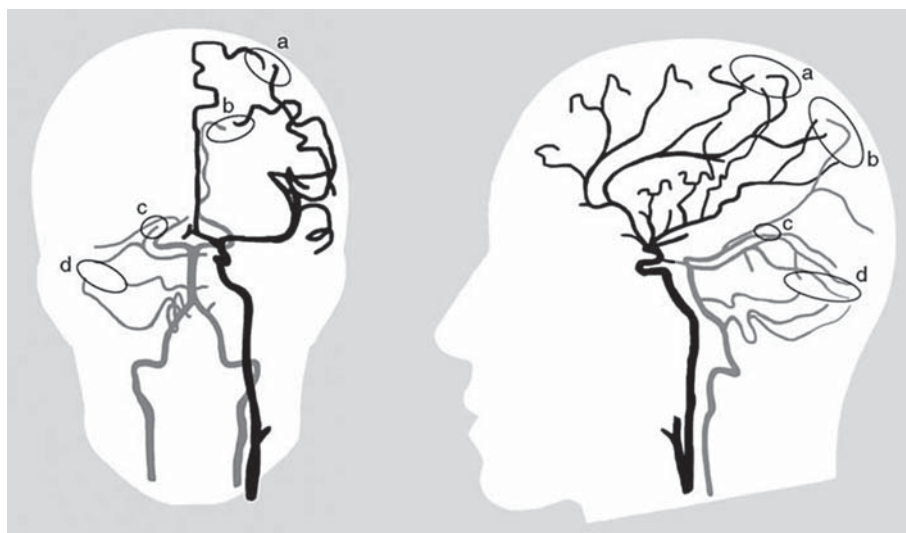
#### *Imaging Perspective on Time*

Defining different time phases for an individual patient is not easy. If a patient presents with already jeopardized cerebral blood flow and there is a malignant pattern evidenced on initial imaging, even within 1 h of symptom onset, such a case should no longer be considered 'acute' as there are no therapeutic opportunities. So how should we define 'acute'?

If there is an opportunity to evaluate a patient with imaging at two time points and measure the time-to-imaging in a series of patients and put it in a graph of brain tissue loss versus time, each individual patient will have a different curve or time course of ischemic injury. Likewise, serial imaging in stroke patients, who are managed conservatively, may demonstrate that each patient is slightly different as they have their own disease course. With the aid of imaging, those patients who need early and aggressive intervention may be identified earlier.

#### *Flow Determines Time*

The amount of collateral flow and its capacity to compensate for hypoperfusion governs time; it determines the time from vascular occlusion to the onset of symptom, the nature of



**Fig. 2.** Diagram of leptomeningeal collaterals, bridging the anterior and middle cerebral arteries (a), the posterior and middle cerebral arteries (b), the superior and posterior cerebral arteries (c), and the major cerebellar hemispheric arteries (d).

symptoms (e.g. fluctuating or stuttering course) and it also determines when intervention may be necessary.

The significance of cerebral blood flow may not merely define such time points; hemodynamics may actually predict possible outcomes of reperfusion. For instance, a partial middle cerebral artery stroke evolves and leads to infarction in a fractional area of that territory. As time progresses, that area will have increased resistance because of poor inflow and associated venous collapse [1]. As flow is diminished, even if treatment is instituted rapidly, reperfusion may yield an unsatisfactory result or negligible clinical impact. From this perspective, we may realize that addressing time alone may not be sufficient for achieving definitive reperfusion and good clinical outcome.

#### *Continuum and Homeostasis of Flow*

A balance exists between proximal arterial compromise and the corresponding collateral flow. For instance, leptomeningeal anastomoses provide collateral flow to adjacent cerebral and cerebellar arterial territories. Diversion of flow through these diminutive structures allows for retrograde perfusion of the collapsed arterial bed distal to the occlusion (fig. 2) [5].

Shunting at the circle of Willis may be relatively simple in terms of local flow diversion, yet the vast network of leptomeningeal collaterals is quite complex and knowledge remains limited on their function. Leptomeningeal collateral flow is driven by hemodynamic factors such as the pressure gradient between adjacent arterial territories [5, 6]. As retrograde or reverse collateral flow into the occluded arterial territory is driven by the sudden pressure drop downstream from an occlusion, the resultant increased flow through these small anastomoses causes an increase in fluid shear stress (FSS) and a complex chain of events that likely involves release of various cytokines, triggering vascular remodeling [1]. Another mechanism that could contribute to vascular remodeling is hypertension, in which angiotensin II appears to be a critical mediator [7]. Such cerebral arteriogenesis promotes outward growth of anastomoses and eventual accommodation for impairment of flow with normalization of FSS.

Today, advanced technology enables us to use serial imaging to differentiate time curves of an individual patient, discerning collateral recruitment and subsequent fluctuations. Spatial coregistration of serial CT or MRI datasets permits evaluation of serial changes in blood flow with either CT or MRI perfusion in a particular area of brain or voxel. Such approaches can also relate what happens in terms of voxel-based changes for impact of flow on ischemic infarction or hemorrhagic transformation as shown on FLAIR or T2-weighted sequences [8]. As a result, we can predict from one volume of interest of voxel at baseline to other time points, the relationship between changes in blood flow and tissue fate in that particular region, ranging from infarction to hemorrhage or neither.

### *Imaging Infrastructure*

The infrastructure to study the evolution of cerebral ischemia is now available. Many clinicians routinely acquire serial imaging at baseline, after intervention and even during later phases of hospitalization [1]. Although such imaging may not be acquired for a particular research study and simply for clinical indications, such data are extremely valuable for understanding the pathophysiology of stroke.

In stroke trials, imaging has principally been used in secondary roles with respect to outcomes. Imaging addresses exploratory or ancillary aims, yet never eclipses the principal objective of evaluating therapeutic impact of a novel intervention on clinical outcomes. Clinical outcome is always the ultimate priority and imaging features are typically subsidiary to whether novel therapy works or not.

Ideally, prospective imaging data are desired, but retrospective analyses of such imaging data are also useful. It is now feasible to implement large-scale imaging analyses via core laboratory activities and worldwide collaborations.

The decision about acquisition or even collection of routine imaging is limited by funding, as the question of resources always arises. Unfortunately, the focus of every trial is typically about therapeutic intervention and consideration of imaging is frequently discounted. Various funding sponsors, including industrial or governmental, place a different amount of interest on imaging but it is always secondary to determining the clinical impact of a novel therapy. Nonetheless, imaging insurance at the start of a trial may reveal influential pathophysiology even at later phases of clinical trials. Lessons from imaging in phase 2 trials may characterize key mechanisms to target in subsequent phase 3 clinical trials. Quite frequently, however, only limited imaging is obtained to confirm key pathophysiology and subsequent studies often proceed without imaging. Even after a phase 3 clinical trial, the imaging data are disregarded if the trial has been negative, without careful consideration of pivotal determinants [1].

## **Neuroprotection**

The year 2013 marks an important milestone in the history of neuroprotective agents for stroke with the completion of the first prehospital neuroprotection stroke study, the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial [9]. It is time to think about the relationship between neuroprotection and cerebral blood flow, and how these relate to such early drug administration.

### *FAST-MAG Trial*

The FAST-MAG trial aims to demonstrate that paramedic initiated intravenous infusion of magnesium sulfate within 2 h of symptom onset improves long-term functional outcome of stroke patients [10]. The trial was implemented using a voice-over-internet protocol simul-

taneous ring system to enable physician-investigators to obtain consent immediately from competent patients or legally authorized representatives. The trial completed the 1,700th final patient recruitment in December 2012, and preliminary observation of the first 1,470 patients revealed a median interval time of 46 min from symptom onset to drug administration, with 73% of subjects receiving the study drug within 1 h of symptom onset [10].

It is important to consider the initiation of neuroprotection during these early phases as it allows the use of neuroprotectives to freeze or preserve the penumbra without altering the vascular status. The next steps will incorporate neuroprotection with revascularization, and this may provide a platform to synergize neuroprotection with blood flow restoration.

## Thrombolysis

While everyone attempts to extend the time window of thrombolysis, it is recognized that the baseline imaging can actually predict response. Revascularization entails recanalization (i.e. opening up an artery) and reperfusion which signifies reestablishing flow in the downstream territory. It is now possible to look at the effects of thrombolysis on both recanalization and reperfusion with serial use of multimodal CT/MRI. Hyperperfusion and the impact of sudden changes in blood flow may also be studied with respect to sequelae such as hemorrhage.

### *Early and Late – Does Time Matter?*

Recent studies provided some interesting findings related to the role of time duration in cerebral ischemia and the impact of thrombolysis. In a German study, thrombolysis was given in a mobile stroke unit with the overall purpose of initiating revascularization as early as possible to potentially improve associated neurological outcomes; it demonstrated feasibility but in an odd twist, even thrombolysis used at this very early phase, did not result in improved outcomes [11]. This finding suggests that time alone may not guarantee a favorable outcome and that the time effect is modified by the collateral perfusion status.

In another study, looking at the late extreme of the thrombolysis window, the European Cooperative Acute Stroke Study III (ECASS III) trial extended thrombolysis use to 4.5 h based on a very simplistic imaging approach with noncontrast CT scan [12]. ECASS III was a positive study with key results leading to extension of the thrombolysis window to 4.5 h. This positive result emerged only because it was largely driven by the patient subgroup between a time window of 4 and 4.5 h [13]. Additionally, the subgroup of patients with an extended thrombolysis window of 4–4.5 h did far better than either subgroups of 3–3.5 h or 3.5–4 h, without any evidence of a graded relationship with respect to time. A possible explanation to this observation is that these latest patients could be recruited with CT findings that still looked benign, likely reflecting a sustained collateral status. Ironically, it is exactly those patients who one would exclude, due to the restrictive time window alone, yet they benefited the most. In sum, patients with better collateral flow may survive longer without extensive injury and such robust collateral status not only permits, but enhances the effects of reperfusion.

### *Baseline Imaging Patterns Predict Response*

The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study revealed that different imaging patterns may identify patient subgroups that are likely to benefit from reperfusion [14]. Recent data have shown that a malignant DWI pattern may be seen even in patients who present within 4.5 h, at various stages within the standard thrombolysis window [15, 16]. The DEFUSE study also demonstrated that with



perfusion imaging, a substantial percentage of patients have a malignant pattern even within the first few hours of symptom onset. Hence, imaging may be important at these very early stages to identify and possibly exclude malignant profile cases that are likely to have poor flow and poor response to revascularization [14, 15, 17].

### *Serial Imaging*

The Alberta Stroke Program Early CT Score (ASPECTS) is a very useful systematic approach to grade severity of ischemia on CT/MRI, for monitoring serial changes and to evaluate the impact of recanalization and reperfusion [18–20].

Serial noninvasive advanced imaging, such as CT/MRA or perfusion imaging, could be used to chronicle recanalization or the change in arterial patency. Such serial perfusion imaging may demonstrate reperfusion, yet the same technique must be applied at each time point to definitively and accurately document recanalization or reperfusion [21]. This becomes important because one can start to study the parameters mentioned earlier in terms of voxel or region-of-interest-based changes in specific regions of the brain. For example, one can assess serial time-to-maximum (Tmax) changes from baseline to 24 h to delineate Tmax evidence of reperfusion within a given voxel. One can also look individually at how the Tmax changes from one value to the next in a single area of the brain, and each of these gives us a different definition or dimension of reperfusion [8]. Such coregistration of serial imaging techniques may also map voxel fate with respect to hemorrhagic transformation and ischemic infarction. Serial changes on gradient echo sequences can be used to coregister studies at two different time points and map hemorrhagic transformation, the degree of hemorrhage, and to correlate which voxel or specific area is affected. Ischemic infarct evolution is not only about the change in size of lesion growth, or even reversal, but also about predicting the tissue fate of which region stays unchanged, which areas suffer severe injury and which have improved or reversed (fig. 3).

Hyperperfusion can also be readily demonstrated on arterial spin-labeled MRI, whereas it is difficult to detect with standard dynamic susceptibility contrast techniques. Therefore, serial imaging may chronicle the dynamics of territorial perfusion from acute to chronic phases after stroke, and it may provide novel insight on dynamics of reperfusion and hemorrhagic transformation (fig. 4) [22].

## **Reperfusion**

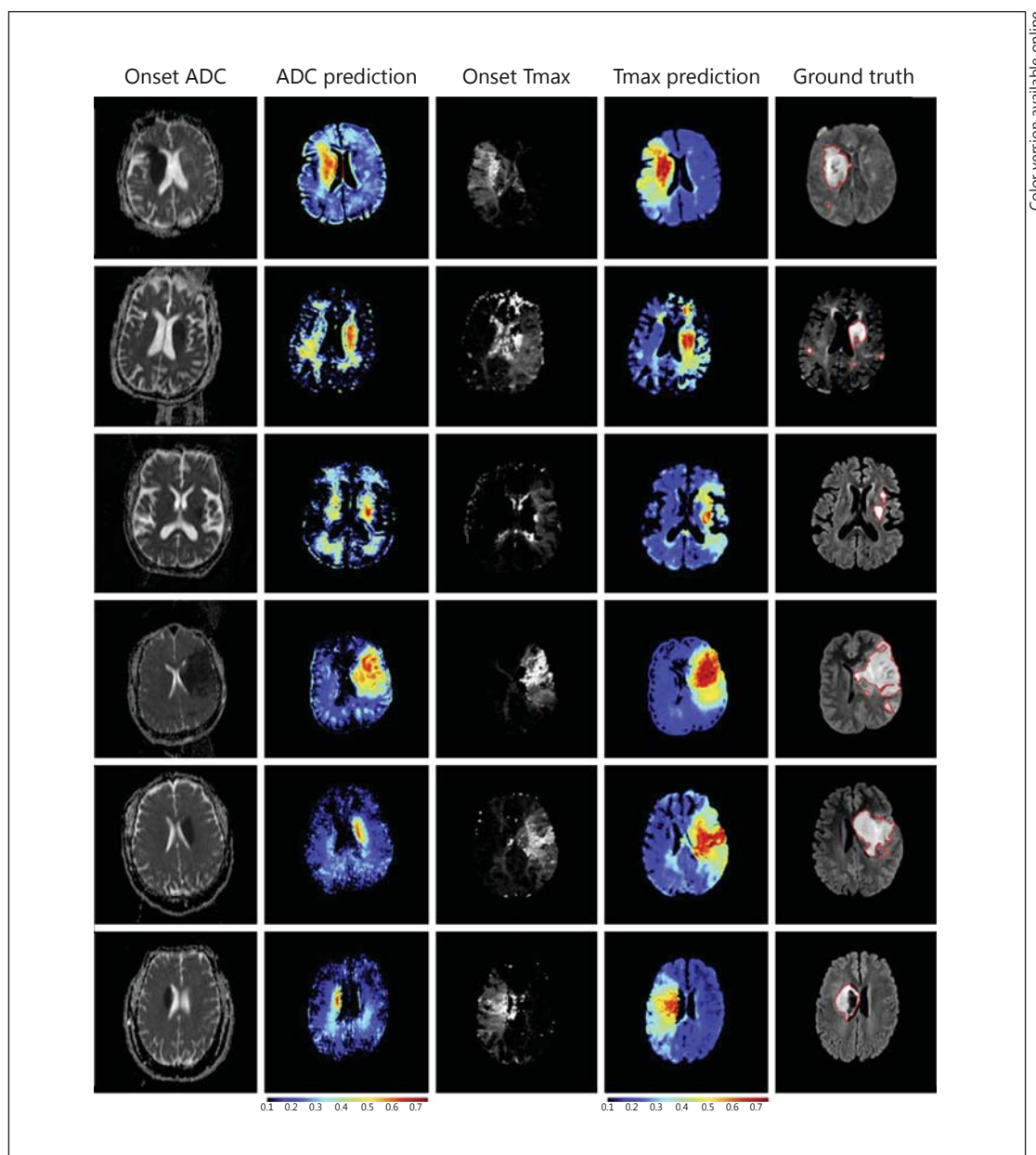
### *Definitive Reperfusion*

It is possible to measure the amount of reperfusion in downstream tissue using the Thrombolysis in Cerebral Infarction (TICI) score on angiography. However, definitive or optimal reperfusion needs to be defined based on associated clinical outcomes. Different therapies are currently used for achieving reperfusion or revascularization, and the effects of these different approaches can be evaluated with serial imaging. Such information may be used to define optimal or definitive reperfusion in terms of serial imaging correlation with clinical outcome, instead of focusing solely on angiographic success.

### *TICI and ASITN/SIR Grading Scales*

To assess angiographic results, the TICI score published in 2003 has been used, with categories of reperfusion ranging from grade 0 to 3; the higher the grade, the more complete the antegrade perfusion beyond the occlusive lesion [23]. The modified TICI was later introduced and used in various studies such as the Interventional Management of Stroke (IMS) III trial, and it made a key distinction in the subcategory 2, further defined as grades 2a (<50%)

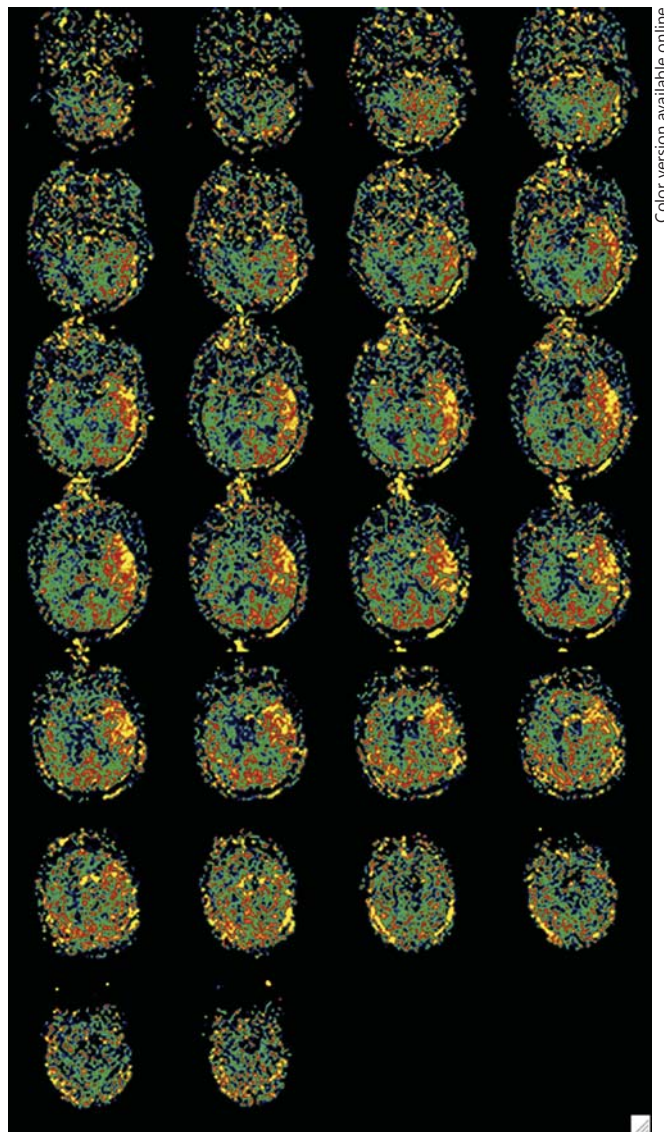




**Fig. 3.** Coregistration of serial imaging studies in predicting tissue fate after ischemic infarction. ADC and Tmax perfusion at onset are illustrated with the corresponding prediction of the models and for 6 patients. Predictions were compared to the ground truth (red contours; color refers to the online version only) manually outlined on follow-up FLAIR at day 4.

and 2b (>50%) [24, 25]. This scoring system is still undergoing revision with consensus recently established in a pending publication endorsed by numerous societies.

Collateral grade has mainly been scored with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral flow grading system [23]. Although it is relatively crude and even suboptimal, it has been a practical system to use and an important one that is most widely employed for this purpose.



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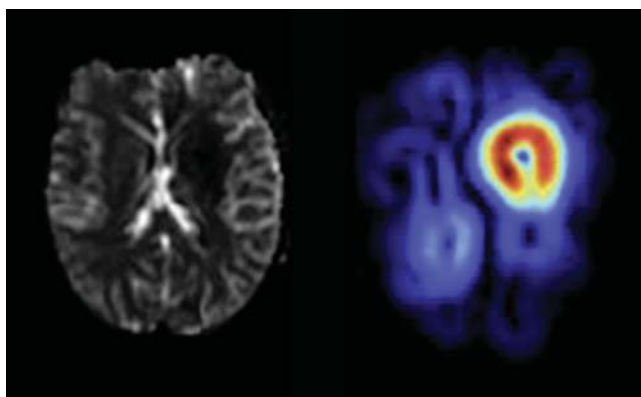
**Fig. 4.** Arterial spin-labeled MRI study demonstrating hyperperfusion in the left middle cerebral artery territory after reperfusion.

#### *Defining Definitive Reperfusion*

The definition of reperfusion was certainly advanced by DEFUSE-2, where the investigators did not just look at baseline patterns but also patterns of reperfusion. They used target mismatch as the main identification for selection of optimal candidates, but there were also separate PWI criteria for reperfusion which was greater than a 50% reduction in PWI (measured as Tmax greater than 6 s) volume at early follow-up and at final angiography, as TICI grades 2b or 3 [15].

Different definitions for reperfusion have been used in other studies such as the Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO) 2 and SOLITAIRE™ FR With the Intention For Thrombectomy (SWIFT) trials, in which successful revascularization was defined as TICI grades 2a, 2b or 3 in TREVO 2 [3] and Thrombolysis In Myocardial Infarction (TIMI) grades 2 and 3 in all treatable vessels in the SWIFT trial [2]. In these two studies, with respect to the successful rate of revascularization, both met their prespecified end point. The outcome measurements, however, were different. The SWIFT

**Fig. 5.** Gradient map of cerebral blood volume illustrating regional variations in this critical perfusion parameter during acute stroke because of left middle cerebral artery occlusion. The circumscribed area of increased gradients around the core offers insight on the potential expansion of ischemic injury into the surrounding penumbra during the ensuing hours.



trial used a novel end point that comprises successful revascularization without symptomatic intracranial hemorrhage [2]. This composite end point was used for the first time to define successful reperfusion. Therefore, it is possible to use a combination of angiographic measures of revascularization or reperfusion as well as intervening tissue events, suggestive of hemorrhage or infarction as it relates to clinical outcome, to refine the definitions used in a trial to best approximate definitive reperfusion.

Definitive reperfusion could be defined based on clinical outcomes, but there is not necessarily an optimal degree of TICI reperfusion that has been identified to date. In addition, the optimal threshold for differentiating TICI grade 2b between the two different systems, TICI and modified TICI, remains unknown. Although SWIFT used symptomatic intracranial hemorrhage as a criterion, it excluded other forms of hemorrhage. It is not known whether other forms of hemorrhage may also need to be considered.

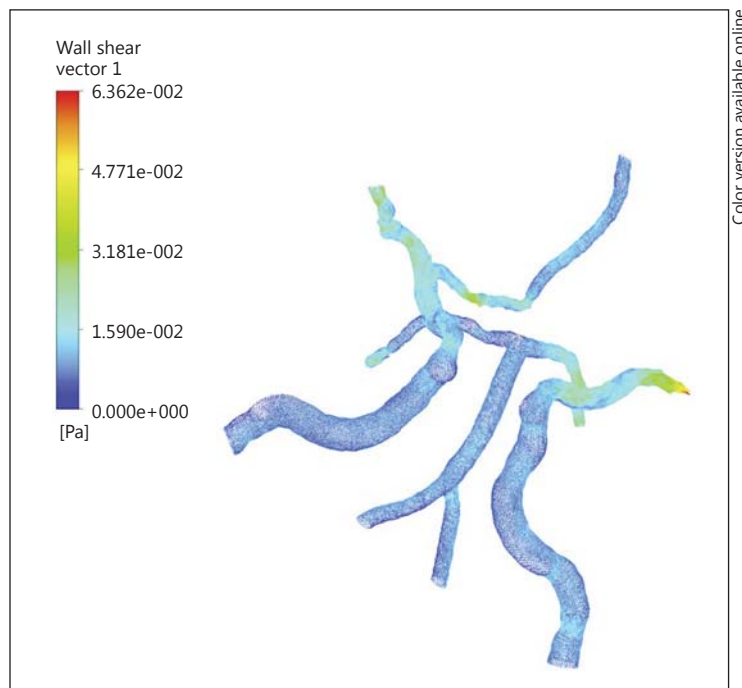
In this context, it is now possible to look at flow from basic pathophysiology to prehospital treatment with neuroprotective agents, from baseline imaging and different combinations of therapy between neuroprotection and revascularization, and also to measure precisely what happens not just after revascularization but also during the subsequent hospital course. For all these purposes, imaging plays a central role in what may be viewed as the future of ischemic stroke to elucidate the importance of flow in treatment of large vessel occlusive disorders.

### Intracranial Atherosclerosis

Up to now, the discussion of acute ischemic stroke has mainly focused on clots or the assumption of thromboembolism; intracranial atherosclerosis (ICAS) is another important etiological entity that should not be overlooked. ICAS trials have enrolled patients with recent ischemia, illustrating that blood flow patterns may predict outcome in such patients [26]. Akin to prior discussion of acute ischemic stroke, there is a balance or homeostasis of flow between limited forward flow as measured by the TICI scale and retrograde collateral flow.

A single perfusion imaging provides only snapshots of the dynamic process in the brain and associated vasculature, unlike serial imaging. However, some novel postprocessing techniques permit evaluation of collateral perfusion patterns. The dynamic nature of cerebral blood volume collapse from the core to more peripheral areas at risk may be predicted with novel techniques that detect regional variations or gradients. Cerebral blood volume gradients within a region or arterial territory of the brain may be depicted on a single static imaging study (fig. 5) [27].

**Fig. 6.** CFD model depicting the high (yellow; color refers to the online version only) wall shear stress at the left middle cerebral artery stenosis.



Analysis of collaterals in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study showed that outcome can be strongly and potently predicted based on collateral flow, above and beyond the degree or percentage of luminal stenosis [26]. The importance of percent stenosis, previously regarded as one of the most significant factors, to predict subsequent events is actually negated once collateral flow data are considered. Interestingly, the majority of patients with ICAS that suffer recurrent strokes do not have severe lesions as defined by the degree of luminal caliber reduction. The definition of severe may therefore be reclassified or redefined based on flow and not merely on the percentage of maximal stenosis.

In the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) [28] study, it was shown that blood flow was also an important factor in predicting outcome or early recurrent stroke in the territory. For early recurrent stroke, when there was good collateral flow, in both medical and stenting arms, the rate of recurrence was 0% [29]. This is in accordance with physics dictated by the Hagen-Poiseuille equation that not just the degree of maximal luminal reduction matters but numerous other anatomical features like lesion length, viscosity of blood flow and other factors that may be important as they affect the pressure gradient across the lesion.

All these specific anatomical variables may be difficult to study, yet advanced imaging techniques such as computational fluid dynamics (CFD), may provide excellent details about hemodynamics and the impact of a stenosis or ICAS lesions [28, 30]. Another imaging entity akin to the fractional flow reserve (FFR) measure that has been used in cardiology [31] looks simply at the flow or the degree of pressure drop across a lesion. Such normalized ratios for hemodynamic impact of a given lesion may be used to study mechanisms of arteriogenesis and shear stress in more detailed fashion. FFR was performed originally with maximal vasodilatation by using adenosine [32]. Recently, the approaches have moved away from use of a hemodynamic reserve challenge to noninvasive methods [33]. A novel technique converts digital subtraction angiography from 2D to 3D to create a geometrical mesh that allows for manipulation of the geometry and CFD calculations [34]. The pressure gradient from upstream



to downstream segments across the lesion can thereby be measured from a static biplanar angiogram, using just anteroposterior and lateral views. 3D imaging datasets such as CT/MRA can be used for CFD calculations as well. The changes in pressure across a lesion can be simulated by CFD [35] that can also be used to measure FSS (fig. 6), as FSS is a key factor in maintaining the homeostasis between atherosclerotic plaque vulnerability and elevated FSS of arteriogenesis to compensate for inadequate antegrade flow [36].

## Conclusion

The continuum from acute stroke pathophysiology to more chronic conditions such as ICAS reveals the importance of flow. A framework now exists to properly image the hemodynamics of stroke across such phases. The future of research in this area will be challenging and exciting at the same time. Focus should be emphasizing on reexamination of valuable information available from current imaging techniques, such as time-of-flight MRA, CTA and digital subtraction angiography, and on leveraging these novel technologies, such as CFD, FFR or perfusion imaging, and thus a better simulation of the cerebral hemodynamics and collaterals could be visualized for real.

The balance of antegrade flow and collateral perfusion may affect the likelihood of successful reperfusion, the likelihood of infarction or ischemic evolution, the probability of hemorrhagic transformation and most importantly, subsequent clinical outcome. To date, despite the lack of focus with respect to blood flow and the relationship with ischemia, we now have the framework to study hemodynamics with multimodal imaging techniques. Such approaches may reveal much more about ischemic stroke and enable us to do more for our patients in both the acute and chronic stages, across different disorders with thromboembolic and atherosclerotic mechanisms.

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